

**REMARKS/ARGUMENTS**

Claims 1-42 are pending in this application. Claims 12, 23, 28, 32, and 39 have been amended without prejudice or acquiescence. Support for the amendments can be found throughout the specification and more specifically in paragraphs [0010], [0014], and [0020]. No new matter has been added. Applicants retain the right to file a divisional application to any cancelled or nonelected claims. Applicants' species election is made without prejudice or acquiescence. Upon the allowance of a generic claim, Applicants will be entitled to consideration of claims to additional species, provided that all claims to each additional species are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.146.

Attached hereto is a marked-up version of the changes made to the specification as Appendix A and changes made to the claims by the current amendment as Appendix B. A clean copy of all pending claims is marked as Appendix C.

The issues outstanding in the application are as follows:

- Affirmation of election requirement
- Specification objection
- Claims 12-15 and 17-41 were rejected under 35 U.S.C. § 112 as allegedly not being enabled by the specification.
- Claims 1, 7-8, and 42 were rejected under 35 U.S.C. § 102 as allegedly being anticipated by Kircheis.
- Claims 1-4, 7-11, 28-30 and 41 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Johnston *et al.* (U.S. Patent No. 5,703,057) in view of Kircheis *et al.*
- Claims 32-41 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Johnston *et al.* (U.S. Patent No. 5,703,057) in view of Kircheis *et al.* and Wiener *et al.* (U.S. Patent No. 6,348,449).

### **I. Affirmation of election requirement**

Applicants elect claims 1-42 without prejudice or acquiescence. Applicants hereby affirm election of the species of genes associated with an infectious disease and HIV as a pathogenic viral genome.

### **II. Specification objection**

The specification has been amended and contains no informalities. No new matter has been added.

### **III. Rejection under 35 U.S.C. § 112**

The Examiner has rejected claims 12-15 and 17-41 under 35 U.S.C. § 112 first paragraph as allegedly not being enabled by the specification. Applicants respectfully traverse.

In order to advance prosecution of this application, Applicants have amended claims 12, 23, 28, 32, and 39 without prejudice or acquiescence. No new matter has been added.

Claims 12, 23, 28, 32, 39, and subsequent dependent claims 13-15, 17-22, 24-27, 29-31, 33-38, and 40-41 are enabled by the specification. In light of the amendments, Applicants respectfully request withdrawal of the 35 U.S.C. § 112 rejection of claims 12-15 and 17-41.

### **IV. Rejection under 35 U.S.C. § 102**

The Examiner has rejected claims 1, 7-8, and 42 under 35 U.S.C. § 102 as being allegedly anticipated by Kircheis *et al.* Applicants respectfully traverse.

Patent law requires that “a rejection for anticipation under section 102 requires that each and every limitation of the claimed invention be disclosed in a single prior art reference.” *In re Paulsen*, 30 F.3d 1475, 31 U.S.P.Q. 2d 1671 (Fed. Cir. 1994). Applicants’ invention is not anticipated by Kircheis *et al.*, which does not teach every limitation of claims 1, 7-8, and 42. The broadest reasonable interpretation of the claims must also be consistent

with the interpretation that those skilled in the art would reach. *In re Cortright*, 165 F.3d 1353, 1359, 49 USPQ2d 1464, 1468 (Fed. Cir. 1999).

The term “aggregate protein” as described in the specification on page 8, paragraph [0044], requires that an aggregate protein is “combined to form a large amorphous particle.” A conjugate is nonidentical to an aggregate. Applicants refer the Examiner to the definition of a conjugated protein, paraphrased from the McGraw-Hill Dictionary of Scientific and Technical Terms, p. 439 New York, Fifth Edition, which states that a conjugated protein is defined as a protein combined with a nonprotein group. Thus, a conjugated protein is different and nonidentical to a protein aggregate.

Applicants teach a protein aggregate conjugated to a polycationic polymer in paragraph [0079] on page 14. Furthermore, in paragraph [0117] on pages 23-24, Applicants describe separate conjugation and aggregation protocols, indicating that these processes are nonidentical to Kircheis *et al.* The conjugations performed by Kircheis *et al.*, as on pages 416-417, would not yield protein aggregates, as suggested by the Examiner. The periodate and cyanoborohydride conjugation method used by Kircheis *et al.* first oxidizes transferrin through the reaction with periodate, and then, through the reaction with cyanoborohydride conjugates the amine groups of PEI to the transferrin protein. The resulting conjugate is a single transferrin conjugated to PEI. In the case of Kircheis *et al.*, transferrin does not conjugate to itself to form a protein aggregate through the cyanoborohydride conjugation. Thus, as a conjugate by definition may not contain multiple proteins of the same composition, no aggregate is formed in Kircheis *et al.*, and Applicants’ invention is not anticipated. Likewise, the conjugation process used to link antiCD3 antibodies and PEI is similar to the cyanoborohydride conjugation, and its end product is a single antiCD3 antibody conjugated to PEI, not antiCD3 aggregates, and thus Applicants’ invention is not anticipated. The Examiner merely states that this conjugation process yields protein aggregates, but this opinion of the Examiner, which is unsupported by scientific evidence, is insufficient to support a *prima facie* case of anticipation. Barring any indication in the reference itself that the limitation of the protein aggregate is taught, the burden rests with the Examiner to provide evidence to support this statement. Applicants contend that a proper *prima facie* case of anticipation has not been made because identity is clearly lacking.

Therefore, since the limitation of a protein aggregate is absent in Kircheis *et al.*, Kircheis *et al.* is precluded from anticipating the present claims. Thus, the rejection of claims is improper, and withdrawal of the rejection is respectfully requested.

#### **V. Rejection under 35 U.S.C. § 103(a)**

The Examiner has rejected claims 1-4, 7-11, 28-30 and 41 under 35 U.S.C. § 103 as being allegedly being obvious over Johnston *et al.* (U.S. Patent No. 5,703,057) in view of Kircheis *et al.* Applicants respectfully traverse.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Johnston teaches expression vectors encoding antigens prepared from pathogenic viruses, and the expression of such antigens in mammalian cells. Applicants teach expression vectors, including vectors which express antigens derived from pathogenic viruses for expression in mammalian cells. The Johnston reference does not teach such vectors bound to an aggregated protein polycationic polymer conjugate.

The Kircheis *et al.* reference teaches protein conjugated to polycationic polymers bound to DNA. The Kircheis *et al.* reference does not teach protein aggregates. The Examiner has interpreted that the conjugation process yields transferrin or antiCD3 aggregates. However, this is not the case, for the same reasons as stated above. Additionally, there is no suggestion in Kircheis *et al.* or Johnston that protein aggregates would be desirable. Thus, the combination of Kircheis *et al.* and Johnston does not produce the Applicants' invention, as the protein aggregate is not taught or suggested.

In light of the above arguments, Applicants respectfully request withdrawal of the 35 U.S.C. § 103 rejection.

#### **VI. Rejection under 35 U.S.C. § 103(a)**

Claims 32-41 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Johnston *et al.* (U.S. Patent No. 5,703,057) in view of Kircheis *et al.* and Wiener *et al.* (U.S. Patent No. 6,348,449). Applicants respectfully traverse.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In *re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Johnston teaches expression vectors encoding antigens prepared from pathogenic viruses, and the expression of such antigens in mammalian cells. Applicants teach expression vectors, including vectors which express antigens derived from pathogenic viruses for expression in mammalian cells. The Johnston reference does not teach such vectors bound to an aggregated protein polycationic polymer conjugate. The Kircheis *et al.* reference teaches protein conjugated to polycationic polymers bound to DNA. The Kircheis *et al.* reference does not teach protein aggregates, for the reasons outlined above. The Weiner reference teaches genetic constructs that encode a target protein and further include genes which enhance the immune response, such as cytokines. The Weiner reference does not teach protein aggregates. The combination of Johnston, Kircheis *et al.*, and Weiner does not yield the Applicants' invention, as the protein aggregate is not taught. Additionally, there is no suggestion in any of these references that a protein aggregate is desirable as a DNA delivery method. Thus, absent the teaching or suggestion of all the limitations of the Applicants' invention, the Examiner has failed to establish a *prima facie* case of obviousness.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 06-2375, under Order No. 10004014 from which the undersigned is authorized to draw.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If any issues arise with this application, the Examiner is encouraged to contact the undersigned at (713)651-5407 for quick resolution of such issues.

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Respectfully submitted,

By 

Melissa W. Acosta

Registration No.: 45,872

FULBRIGHT & JAWORSKI L.L.P.

1301 McKinney, Suite 5100

Houston, Texas 77010-3095

(713) 651-5151

(713) 651-5246 (Fax)

### Appendix A

[0086] The following polynucleotide sequences are representative sequences corresponding to HIV, HSV, HCV, influenza virus or RSV genomes or fragments of the genomes and are within the scope of the invention and some are referenced with the corresponding GenBank Accession Numbers [<http://www.ncbi.nlm.nih.gov/Genbank/GenbankSearch.html>]: U23 (SEQ.ID.NO:1); AF041850: SHIV-HXBc2P 3.2, complete (SEQ.ID.NO:3); U12055: HIV-1, isolate LW12.3, lab worker, complete genome (SEQ.ID.NO:4); M76764: SHIV clone 1A11, complete genome (SEQ.ID.NO:5); NC\_001433: Hepatitis C virus, complete genome (SEQ.ID.NO:6); AF290978: Hepatitis C virus isolate colonel complete genome (SEQ.ID.NO:7); NC\_001798: Human herpesvirus 2, complete genome (SEQ.ID.NO:8); NC\_001781: Human respiratory syncytial virus, complete genome (SEQ.ID.NO:10); AF321523: HIV-1 clone MJ4 from Botswana, complete genome (SEQ.ID.NO:11) and K02007: HIV-1, isolate ARV-2/SF2, complete proviral genome; (SEQ.ID.NO:12). One of skill in the art is cognizant that the above sequences are representative sequences of several pathogenic genomes. It is well known and understood that standard methods of molecular biology can be used to isolate and clone a sequence of any pathogen of interest and to use this sequence in the present invention.

**Appendix B**

12. (Amended) A method of producing a DNA [vaccine] composition comprising the step of incubating an expression vector with an aggregated protein-polycationic polymer conjugate to form DNA particles wherein the expression vector comprises a promoter polynucleotide sequence operatively linked to a polynucleotide sequence encoding an antigen.
23. (Amended) A method of treating a condition in [an organism] a mammal by administering to the [organism] mammal the DNA [vaccine] composition of claim 12.
28. (Amended) A method of inducing an immune response in [an organism] a mammal comprising the step of administering to [an organism] the mammal an expression vector bound to an aggregated protein-polycationic polymer conjugate wherein the expression vector comprises a promoter polynucleotide sequence operatively linked to a polynucleotide sequence encoding an antigen.
32. (Amended) A method of inducing an immune response in [an organism] a mammal comprising the step of co-administering to [an organism] the mammal [an expression vector] two expression vectors, both bound to an aggregated protein-polycationic polymer conjugate wherein the first expression vector comprises a promoter polynucleotide sequence operatively linked to a polynucleotide sequence encoding an antigen and the second vector comprises a cytokine expression vector .
39. (Amended) A method of inducing an immune response in [an organism] a mammal comprising the step of administering to [an organism] the mammal an expression vector bound to an aggregated protein-polycationic polymer conjugate wherein the expression vector comprises a first promoter polynucleotide sequence operatively

linked to a first polynucleotide sequence encoding an antigen and a second polynucleotide sequence encoding a cytokine.



### Appendix C

1. A composition comprising an expression vector bound to an aggregated protein-polycationic polymer conjugate, wherein the expression vector comprises a promoter polynucleotide sequence operatively linked to a polynucleotide sequence encoding an antigen.
2. The composition of claim 1 wherein the polynucleotide sequence encoding the antigen is a fragment of a genome or gene selected from the group of genomes or genes associated with a disease consisting of infectious disease, cancer, and autoimmune disease.
3. The composition of claim 2 wherein the polynucleotide sequence encoding the antigen is a fragment of a genome or gene selected from the group of pathogenic genomes consisting of virus, bacterium, fungus and protozoa.
4. The composition of claim 3 wherein the polynucleotide sequence encoding the antigen is a fragment of a genome selected from the group of viral genomes consisting of HIV, HSV, HCV, influenza and RSV.
5. The composition of claim 2 wherein the polynucleotide sequence encoding the antigen is a fragment of a gene selected from the group of genes associated with an autoimmune disease consisting of rheumatoid arthritis, vasculitis, and multiple sclerosis.
6. The composition of claim 1 wherein the aggregated protein is albumin.
7. The composition of claim 1 wherein the polycationic polymer is selected from the group consisting of polyamino acids, polyimines or a combination thereof.

8. The composition of claim 7 wherein the polyimine is polyethyleneimine.
9. The composition of claim 1 wherein the expression vector contains a heterologous mammalian targeting sequence.
10. The composition of claim 9 wherein the heterologous mammalian targeting sequence is ubiquitin or a signal sequence for secretion.
11. The composition of claim 10 wherein the signal sequence for secretion is human growth hormone.
12. A method of producing a DNA composition comprising the step of incubating an expression vector with an aggregated protein-polycationic polymer conjugate to form DNA particles wherein the expression vector comprises a promoter polynucleotide sequence operatively linked to a polynucleotide sequence encoding an antigen.
13. The method of claim 12 wherein the polynucleotide sequence encoding the antigen is a fragment of a genome or gene selected from the group of genomes or genes associated with a disease consisting of infectious disease, cancer, and autoimmune disease.
14. The method of claim 13 wherein the polynucleotide sequence encoding the antigen is a fragment of a genome selected from the group of pathogenic genomes consisting of virus, bacterium, fungus and protozoa.
15. The method of claim 14 wherein the polynucleotide sequence encoding the antigen is a fragment of a genome selected from the group of viral genomes consisting of HIV, HSV, HCV, influenza and RSV.

16. The method of claim 13 wherein the polynucleotide sequence encoding the antigen is a fragment of a gene selected from the group of genes associated with an autoimmune disease consisting of rheumatoid arthritis, vasculitis, and multiple sclerosis.
17. The method of claim 12 wherein the expression vector contains a heterologous mammalian targeting sequence.
18. The method of claim 17 wherein the heterologous mammalian targeting sequence is ubiquitin or a signal sequence for secretion.
19. The method of claim 18 wherein the signal sequence for secretion is human growth hormone.
20. The method of claim 12 wherein the polycationic polymer is selected from the group consisting of polyamino acids, polyimines or a combination thereof.
21. The method of claim 19 wherein the polyimine is polyethyleneimine.
22. The method of claim 12 wherein the aggregated protein is albumin.
23. A method of treating a condition in a mammal by administering to the mammal the DNA composition of claim 12.
24. The method of claim 23 wherein the administration of the vaccine is to a mucosal surface.
25. The method of claim 24 wherein the mucosal surface is selected from the group consisting of intranasal surface, oral surface, gastrointestinal and genitourinary tract surface.
26. The method of claim 23 wherein the vaccine is administered parenterally.

27. The method of claim 26 wherein the administration is intraperitoneal, intravenous, subcutaneous, intramuscular and intradermal.
28. A method of inducing an immune response in a mammal comprising the step of administering to the mammal an expression vector bound to an aggregated protein-polycationic polymer conjugate wherein the expression vector comprises a promoter polynucleotide sequence operatively linked to a polynucleotide sequence encoding an antigen.
29. The method of claim 28 wherein the immune response is systemic.
30. The method of claim 28 wherein the immune response is mucosal.
31. The method of claim 28 wherein the immune response is both systemic and mucosal.
32. A method of inducing an immune response in a mammal comprising the step of co-administering to the mammal two expression vectors, both bound to an aggregated protein-polycationic polymer conjugate wherein the first expression vector comprises a promoter polynucleotide sequence operatively linked to a polynucleotide sequence encoding an antigen and the second vector comprises a cytokine expression vector .
33. The method of claim 32 wherein the cytokine expression vector contains the sequence for GM-CSF.
34. The method of claim 32 wherein the cytokine expression vector contains the sequence for IL12.
35. The method of claim 32 wherein the co-administration is to a mucosal surface.

36. The method of claim 35 wherein the mucosal surface is selected from the group consisting of intranasal surface, oral surface, gastrointestinal surface and genitourinary tract surface.
37. The method of claim 32 wherein the co-administration is parenterally.
38. The method of claim 37 wherein the administration is intramuscular and intradermal.
39. A method of inducing an immune response in a mammal comprising the step of administering to the mammal an expression vector bound to an aggregated protein-polycationic polymer conjugate wherein the expression vector comprises a first promoter polynucleotide sequence operatively linked to a first polynucleotide sequence encoding an antigen and a second polynucleotide sequence encoding a cytokine.
40. The method of claim 39, wherein the first and second polynucleotide sequences are under transcriptional control of the same promoter polynucleotide sequence.
41. The method of claim 39, wherein the first and second polynucleotide sequences are under transcriptional control of different promoter polynucleotide sequences.
42. A method of introducing genes into a cell comprising the steps of: forming a DNA particle comprising an expression vector bound to an aggregated protein-polycationic polymer conjugate wherein the expression vector comprises a promoter polynucleotide sequence operatively linked to a polynucleotide sequence encoding an antigen; and incubating the cells with the DNA particle under conditions wherein the cells take in the DNA particle.

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**Sybil P. Parker**

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